Simplified Mathematical Models of Avascular And Vascular Tumor Growth

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Tumors become especially dangerous after they induce blood vessel growth, because the new blood vessels can not only carry oxygen and nutrition that further facilitate tumor growth but also act as passages for tumor cells to spread to other sites of the body. Thus tumor growth can be divided into two phases: avascular and vascular growth. We present two simple mathematical models, 1) to understand the mechanism behind the growth saturation of avascular tumors by investigating two different hypotheses, and 2) to predict the growth of tumor around blood vessels, or perivascular cuffs.

Avascular tumor models have been studied extensively, either on a macro-level chemical distribution[2] or on a microscopic cellular level, and recently both[3]. Although almost all studies reach similar conclusions that avascular tumor can only grow up to a limited size, the saturation mechanisms that are assumed in different models are not the same. We will use a continuous macroscopic-level model to investigate how growth of avascular tumor is related to the chemical concentrations in the environment that tumor lives in. In order to simplify the model, we only consider two cell status, proliferating and necrotic, and only oxygen for the chemical environment. Oxygen concentration distribution is governed by the diffusion-consumption equation

$$\frac{\partial O}{\partial t} = D_O \Delta O - consumption$$

satisfying boundary conditions

$$\begin{aligned} O(r_0-) &= O(r_0+), \quad O'(r_0-) = O'(R_0+), \\ O(r_0) &= O_R \end{aligned}$$

where D_O is the diffusion coefficient, R_0 are the outer radius of the tumor spheroid and r_0 is the radius of the necrotic core. This is a moving boundary problem since the boundary conditions are defined on parameters r_0 and R_0 that change over time, according to the following rules.

- Change of inner radius r_0 due to necrosis: All cells with O below some threshold die, and radius of necrotic core increases.
- Change of outer radius R_0 due to proliferation: All the cells with O above the threshold divide with a constant rate, and thus increase the outer boundary of the tumor spheroid.

$$4\pi R_0^2 \frac{dR_0}{dt} = \frac{dV}{dt} = \int_{r_0}^{R_0} P(4\pi r^2) dr$$

where P is the proliferation rate. Using this model, we show that oxygen supply alone cannot be responsible for the stop of growth, because as tumor grows in size, there is a lower bound for the width of the viable rim that can be healthily supplied by oxygen (See Figure 1). What would happen is that, eventually the necrotic core grew at the same rate as the whole spheroid, leaving the width of the proliferating rim unchanged, but the growth could not stop.

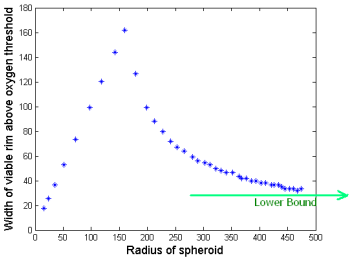

Figure 1: Width of viable rim that can be healthily supported by oxygen

Two saturation hypothesis are tested. One is the cell shedding mechanism, claiming that the newly divided cells on the surface of the tumor can shed away from the tumor spheroid after the tumor grows beyond some size $\bar{R}$ [3]. If this is the only reason for the growth to stop, we observe sudden stop at $R = \bar{R}$, as shown in Figure 2(a).

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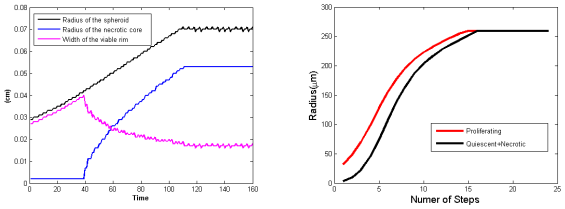
Another possible mechanism is the inhibitory factor that is known to be secreted by cells under severe stress [4]. The inhibitor factor can drive proliferating cells into a quiescent state where cells are less active and consumes less. Since we did not include quiescent cell status explicitly in the model, we combine quiescent and necrotic states as one group. The result is that the thickness of the proliferating rim gradually decreases to zero (See Figure 2(b)), and tumor growth stops because there is no more proliferating cells in the tumor.



(a) Stop of growth due to cell shedding alone, and here $\bar{R} = 0.07cm$

(b) Stop of growth due to inhibitory factor

Figure 2: Growth of tumor radius over time

The vascular tumor growth is much more complicated due to the complex structure of the blood vessel network, which makes pure mathematical analysis impossible. Again, hoping to get some insight of the problem without the cost of numerical simulations, we simplified the problem to only have parallel blood vessels. In particular, in the case of perivascular tumor, where a tumor grows around a single blood vessel, the larger the tumor is, the lower oxygen concentration there is at the outer boundary of the tumor. Figure 3 show the oxygen distribution curves in tumors of different sizes, where the red dots indicate the radii of the tumors. If the threshold of oxygen concentration for tumor cells to die is $0.02mM/cm^3$ (extracted parameter from [3]), then Figure 3 show a supported tumor size of about 110 microns which is consistent with experimental measurement [1].

In vivo, tumors are surrounded by healthy tissues instead of growing in vacuum. Simulation with the model shows that tumor growth can result in invasion of the surrounding healthy tissues by depriving the oxygen supply.

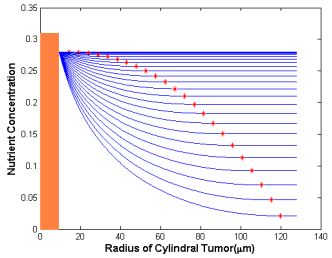


Figure 3: Oxygen concentration distribution in the cylindrical tumor that grows around the blood vessel. Radius of tumor are marked by red stars

In conclusion, we used a simplified continuous mathematical model to describe tumor growth, and for simplicity only oxygen distribution is considered as an exterior factor to influence tumor growth. Compared to multicellular models, it is much cheaper to simulate. Using such a model, we tested two saturation hypotheses for avascular tumor growth separately. In vivo, it should be a combination of the mechanisms that all together contribute to the stop of growth, and we are on the way of putting them together. Since mechanical force can also play a role in regulating tumor cell growth, we also would like to consider including mechanical factors into the model as a future direction.

Acknowledgements

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